Simple Oxazolidine Chiral Diene Ligands for Enantioselective Rh-Catalyzed Conjugate Additions.

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Abstract: Simple oxazolidine-based chiral diene ligands, ultimately derived from serine, have been synthesized using the Seebach self-regeneration of stereocentres strategy. The ligands have been used in the enantioselective Rh-catalyzed conjugate-addition of aryl boronic acids to cyclohexenone. An efficient "*in vacuo"* reaction protocol has been developed as part of this study.

Key words: Diene, Chiral, Enantioselective, Rhodium, Oxazolidine

In recent years, there has been a pronounced level of interest in the design, synthesis and evaluation of chiral diene ligands for enantioselective transition metal-catalyzed transformations.[1] Originally, Hayashi reported that rigid bicyclic dienes, such as **1**[2] (Figure 1), acted as excellent chiral ligands for Rh(I)-catalyzed processes. Whilst ligand **1** is clearly a very effective ligand for asymmetric synthesis, accessing **1** is somewhat involved, including resolution of the racemic diene ligand. The report of **1** prompted the exploration of new areas of chemical space, and other laboratories accordingly sought to design efficient syntheses of new diene ligands avoiding the requirement for resolution. For example, the Carreira laboratory synthesized **2**[3] from readily available chiral pool sources.

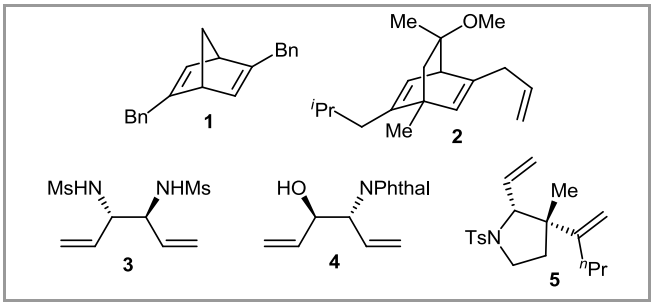
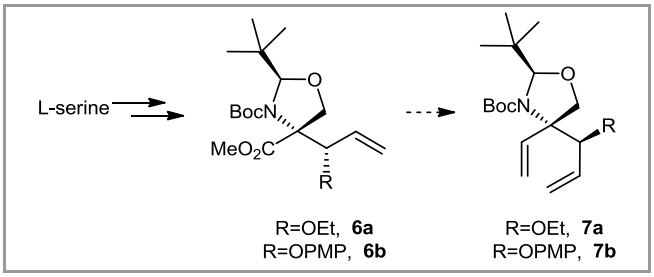


Figure 1 Representative chiral diene ligands.

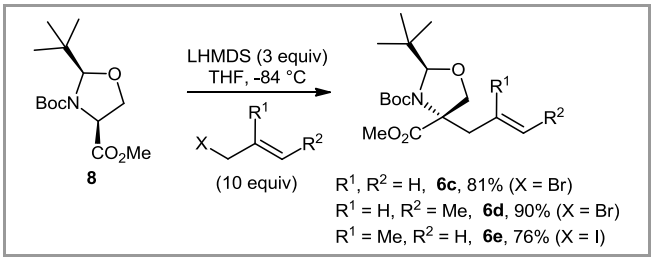
The rigid bicyclic scaffold of ligands **1** and **2** is arguably the key to their success in asymmetric synthesis contexts, therefore it is perhaps surprising that chiral diene ligands which offer much greater levels of conformational flexibility should act as competent ligands. Du has extensively reported on the synthesis and application of "simpler" ligand structures, for example, ligand **3**[4] (Figure 1). Recently, the groups of Trost[5] and Yu[6] have reported asymmetric syntheses of ligands **4** and **5** respectively using transition-metal catalysis, however, in the case of **5**, this ligand was not accessed as a single enantiomer. We felt that a significant level of structural scope existed to examine new ligand structures with syntheses offering diversity and if possible, both enantiomers accessible from inexpensive enantiopure chiral pool sources.

As part of our interest in synthesizing biologically relevant α-[7] and β-amino acids,[8] we have recently reported the use of serine-derived oxazolidines as highly stereoselective motifs for Ireland-Claisen rearrangements.[9] The products from this rearrangement were unsaturated derivatives of biologically important unsaturated β,β′-dihydroxy α-amino acid products, offering large levels of structural diversity of alkyl- and aryl-allyl ethers, with allyl ethers **6a-b** being representative (Scheme 1). We anticipated that ethers such as **6**, derived from serine,[10] could be readily transformed to diene ligands **7a-b** as depicted in Scheme 1.



Scheme 1 Design principle for oxazolidinyl chiral diene ligands.

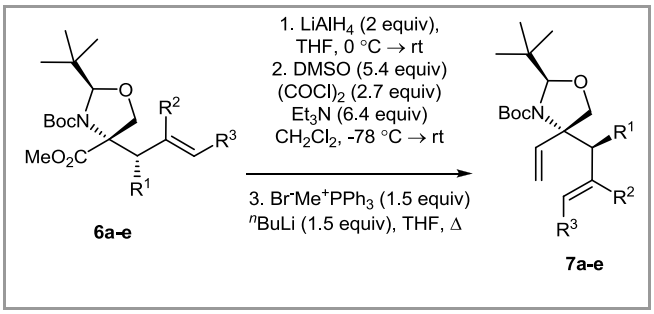
Prior to synthesizing **7a-b**, esters **6a-b** were complemented by three additional esters (**6c-e**) formed by the alkylation of **8** (Scheme 2). These additional ligands would offer the ability to probe steric and electronic sensitivity of the ligands in addition to being potentially simpler to synthesize. Accordingly, LHMDS-mediated enolization and subsequent reaction with electrophile formed oxazolidines **6c-e** in excellent yield.[11,12]



Scheme 2 Oxazolidine alkylations

Oxazolidines **6a-e** have been converted to diene ligands **7a-e** through a synthetic sequence comprising of $LiAlH_4$-mediated ester reduction, Swern oxidation and Wittig olefination (Table 1). It is worth noting that this three-step sequence was synthetically amenable, with only a single chromatographic purification required after the final Wittig methylenation reaction

Table 1 Ligand Synthesis

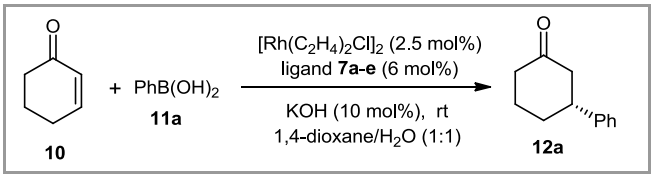


Entry	R^1	R^2	R^3		Yield (%)[a]
1	OEt	H	H	**7a**	68
2	OPMP	H	H	**7b**	53
3	H	H	H	**7c**	58
4	H	Me	H	**7d**	41
5	H	H	Me	**7e**	60

[a] Isolated yield over three steps.

With five diene ligands synthesized, we sought to determine their efficacy in an enantioselective transformation. The Rh-catalyzed addition of phenylboronic acid (**11a**) to 2-cyclohexenone (**10**) was chosen as this reaction arguably acts as the benchmarking evaluation in the area of chiral diene ligand design. The conditions reported by Yu were chosen as a starting point because of the structural similarities of the ligands, *i.e.* the 5-membered ring skeleton in **5** and **7**.[6] In conducting the ligand screen it was observed that the reactions were proceeding sluggishly, and extended reaction times failed to achieve full conversion. Importantly though, on solvent removal at reduced pressure, any residual starting material was consumed. Consequently, a new operationally simple procedure was developed whereby on addition of **10**, the reaction mixture was transferred to a rotary evaporator. The results from this ligand screen are presented in Table 2.

Table 2 Ligand Screening



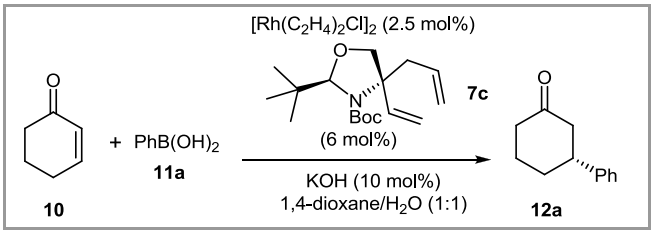
Entry	Ligand[a]	Yield (%)	ee (%)[b]
1	**7a**	100	83
2	**7b**	86	72
3	**7c**	100	87
4	**7d**	40	84
5	**7e**	78	49

[a] Complexation of Rh-catalyst with ligand 7 conducted at 50 °C prior to reaction. [b]Assayed using chiral stationary phase HPLC (Chiralpak AD column).

The reaction is sensitive to the choice of ligand, both in terms of reaction efficiency and enantioselectivity. The reaction is inhibited when the ligand features the methyallyl fragment (**7d**, entry 4, Table 2) and enantioselectivity is reduced when the ligand features the crotyl fragment (**7e**, entry 4). The best combination was seen when the simple ligand (**7c**, entry 3) was used.

Having identified **7c** as the most stereoselective ligand option during the initial benchmarking process, we looked to further explore the reaction optimization (Table 3). Many literature reports specify 50 °C as the optimum temperature to allow catalyst/ligand exchange.[1] However, utilizing our *in vacuo* conditions, it can be seen that this can be done at room temperature with no loss in yield, and a slight increase in enantioselectivity (entries 1 & 2). Moreover, this removes the need to allow the reaction mixture to cool prior to addition of **10**. Under normal reaction conditions (that is, stirring under an inert atmosphere), the reactions proceed sluggishly, even with extended reaction times (entries 3 and 4). However, on heating to 100 °C, it is driven to completion, and a near quantitative yield is obtained (entry 5). Unfortunately, the enantioselectivity is lower than that seen under rotary evaporation.

Table 3 Further Reaction Optimization



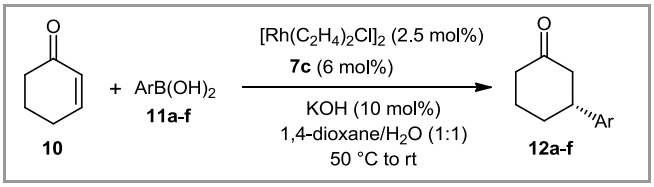
Entry	T (°C)	t	Yield (%)	ee (%)[d]
1[a, b]	20	1 min	100	87
2[b]	20	1 min	100	88
3[c]	20	2.5 h	17	83
4[c]	20	24 h	16	88
5[c]	100	2.5 h	97	82

[a] Complexation of Rh-catalyst and ligand 7 conducted at 50 °C prior to reaction. [b] Reaction transferred immediately to rotary evaporator, set to 40 °C, on addition of **10**. [c] Reaction subjected to

aqueous work-up. [d] Assayed using chiral stationary phase HPLC (Chiralpak AD column). See Supporting Information for details.

Finally, a short study of boronic acid reaction partners has been accomplished (Table 4). In the small sample set presented, ligand **7c** is seen to offer good enantioselectivity with the highest observed selectivity observed with 4-fluorobenzeneboronic acid (91% ee, entry 2, Table 4). The isolated yield of the product derived from 4-acetylbenzeneboronic acid (**12e**) is notably lower, even though the enantioselectivity remains high (entry 5, Table 4).

Table 4 Boronic Acid Scope



Entry	Ar	Yield (%)	ee (%)[a]
1	H	100 (**12a**)	88
2	4-FC_6H_4	95 (**12b**)	91
3	4-$MeOC_6H_4$	93 (**12c**)	84
4	1-Naphthyl	100 (**12d**)	73
5	4-AcC_6H_4	24 (**12e**)	79
6	4-ClC_6H_4	87 (**12f**)	83

[a] Assayed using chiral stationary phase HPLC. See Supporting Information for details.

A solution of phenylboronic acid (1.5 equiv), bis(ethylene)rhodium(I) chloride dimer (2.5 mol%) and ligand **7c** (6 mol%) in 1,4-dioxane (0.9 mL) was allowed to stir at room temperature for 15 minutes. To this reaction mixture was added 2-cyclohexenone and KOH (aq. 0.075 M, 10 mol%) and the reaction mixture immediately concentrated *in vacuo* at a temperature of 40 °C. Subsequent purification by flash chromatography to (10:1 Pet/EtOAc) afforded ketone **12a** as a colourless oil (58 mg, 100%, 88% ee). Chiral stationary-phase HPLC analysis performed using a Chiralpak AD column (hexane/2-propanol, 99:1, 0.5 mL/min, 214 nm); t_R: 23.3 min (minor), 27.8 min (major). $[\alpha]_D^{20}$ +16.0 (*c* 1.88, $CHCl_3$), lit.[13] $[\alpha]_D^{20}$ +17.2 (*c* 1.0, $CHCl_3$, 94% ee); ^1H NMR (500MHz, $CDCl_3$) δ_H 1.74–1.93 (2H, m), 2.07–2.14 (1H, m), 2.17 (1H, ddd, *J* = 13.0, 6.3, 3.2 Hz), 2.35–2.65 (4H, m), 3.03 (1H, tt, *J* = 11.8, 3.9 Hz), 7.22–7.28 (3H, m), 7.35 (2H, app. t, *J* = 7.5 Hz); ^{13}C NMR (125MHz, $CDCl_3$) δ_C 25.6, 32.8, 41.2, 44.8, 49.0, 126.6, 126.7, 128.7, 144.4, 211.0. All analytical data in accordance with reported literature values.

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In conclusion, simple chiral diene ligands have been synthesized from serine. The optimum ligand in this study (**7c**) is synthesized *via* a self-regeneration of stereocenters approach *via* allylation of a serine-derived oxazolidine. As both enantiomers of serine are commercially available and inexpensive, both enantiomers of these ligands will be accessible.

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